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Subject: Reports from Agricultural Research Projects Funded by the U.S.-Israel Binational Science Foundation (BSF)

To: National Agricultural Library
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We are enclosing for your disposition a copy of comments, and Final Report from BSF Research Project No. 804 entitled, "The interaction of high sucrose intake and genetics on generation of diabetes and its vascular complications in man."

for Ernest P. Imle
Assistant Chief

2 Enclosures

UNITED STATES DEPARTMENT OF AGRICULTURE
SCIENCE AND EDUCATION ADMINISTRATION

FEDERAL RESEARCH
NORTHEASTERN REGION
BELTSVILLE AGRICULTURAL RESEARCH CENTER
BELTSVILLE, MARYLAND 20705

September 13, 1978

Subject: Final Report "The Interaction of High Sucrose Intake and Genetics on Generation of Diabetes and Its Vascular Complications in Man"

To: E. P. Imle, Assistant Director, IPD

This report presents the results of an imaginative human study in which the interaction between dietary and genetic factors are related to the incidence of diabetes. The most important finding from this study is that in Yemenite Jews with the same genetic susceptibility toward diabetes, those showing symptoms of diabetes were consuming significantly greater amounts of simple sugars than those not showing evidence of the disease. Intake of simple sugars was the only dietary factor consistently equated with the incidence of diabetes. It was also noteworthy that in individuals with no genetic predisposition toward diabetes, there was no effect of high sugar consumption. These results point out the importance of individual genetic differences in formulating dietary recommendations. The results also support the concept that carbohydrate-sensitive individuals or pre-diabetics are at a higher risk of high levels of sugar intake than the general population. The author should be congratulated on a well-conceived and conclusive study.

There is one technical error in the report. On page 3, paragraph 1, line 4, the magnitude of the ponderal index is incorrectly equated with overweight and underweight.

Walter Mertz
Chairman
Nutrition Institute

Name of Institution The Hebrew University of Jerusalem

U.S.-Israel Binational Science Foundation
P.O.B. 7677
Jerusalem, Israel

Date January 17, 1978

Re: SCIENCE REPORT

1. BSF No. of Proposal: 804

2. Project's starting date*: 1.4.75

3. Project's Duration**: 2 years

4. Type of Report: Annual _____ Comprehensive _____ Final x

5. Title of Proposal: The interaction of high sucrose intake and genetics on generation of diabetes and its vascular complications in man.

6. Name of Principal Investigator(s): Prof. A.M. Cohen

7. Name of Cooperating Investigator and his Affiliated Institution:

Dr. S. Reiser: Carbohydrate Nutrition Lab., Nutrition Institution, U.S.D.A., A.R.S., Bethesda, Maryland

In accordance with our research grant agreement for this project, we herewith submit 5 copies of the above-indicated report.

Signatures

Principal Investigator(s)

Prof. A.M. Cohen

Institution's Authorizing Official

Michael Schiffer

* Project's starting date as stated in the research grant agreement.
** As notified by BSF.

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List of Abbreviations

EDTA - Ethylenediaminetetra-Acetic Acid.

P.I. - Ponderal Index, Height (inches)/$\sqrt[3]{\text{weight (pounds)}}$.

X^2 - Chai square.

HDL - High density lipoproteins.

VLDL - Very light density lipoproteins.

LDL - Light density lipoproteins.

(r) - regression analysis.

i.v. - intravencus.

Abstract

I. Re-study of 402 "new immigrant Yemenite" Jews, who on arrival to Israel 25 years ago had no diabetes, revealed now 12.4% of diabetes (males - 13.9%, females - 10.0%). Overweight in females is associated with increased prevalence of diabetes in all age groups while in males in older age only. The male/female diabetic ratio was greater in overweight than in underweight. Most diabetics had delayed insulin response, however, in 47% of diabetics as well as non-diabetics the peak was at 60 minutes, with a similar extent of insulin response.

II. Plasma triglycerides, cholesterol and LDL levels in diabetics were higher than in non-diabetics, especially in overweight males. Hyperlipoproteinemia prevailed in 27.7% of diabetics versus 11.0% of non-diabetics. The HDL/LDL cholesterol ratio was significantly reduced in overweight diabetics, suggesting the additive coronary risk factor of obesity to diabetes.

III. Dietary study in diabetics and controls suggests two groups (as observed in our studies in the laboratory). One, that on high refined sugar consumption develops diabetes while its relatives with the same genetics, consuming smaller amounts of refined sugars, will not. The second group, who on consuming large amounts of refined sugars will not develop diabetes.

Our dietary-studied group is small in order to establish these results. Such a combined genetic/dietary study should be extended in this group and repeated in other ethnic groups.

Introduction

Yemenite Jewry constitutes a specific ethnic group with a special physique, mode of life and food habits. Upon their arrival to Israel 25 years ago almost no diabetes was detected in them, Cohen, 1961 (1). On examining the old settled Yemenites who lived in Israel for 25 years and over, it was found that the prevalence of diabetes was as high as among immigrants from Western countries. Similarly, the mortality rate from coronary heart disease has markedly increased in this ethnic group since their arrival in Israel, Cohen and Eisenberg, 1974 (2).

A dietary study revealed that while in Yemen almost no sucrose was consumed by them. In Israel the old settled Yemenites' sugar intake was as high as in Western countries, Cohen, 1961 (3). In 1961 we suggested the correlation of high sugar intake and the increase in the prevalence of diabetes. To substantiate this hypothesis we genetically selected two strains of rats, one that on a high refined sugar (sucrose, Cohen, 1972 (4) fructose, Cohen, 1977 (5), or glucose, Cohen, in press, Hormone and Metabolic Research (6)), diet will develop diabetes and diabetic vascular complications while their siblings fed starch will remain normal. The second strain fed on a high refined sugar diet will not develop diabetes. We have suggested that this model may explain the contradicting results in the literature concerning the correlation of sugar intake and the prevalence of diabetes, Cohen, 1974 (7). Increased rates of diabetes where sugar intake has increased have also been observed in other populations: in Asians and Bantu in South Africa, Campbell, 1963 (8), and in South America and Asia, West, 1971 (9), however, no such relationship was found by other authors, (West, 1975 (10), Poon-King, 1968, (11), Kahn, 1971 (12)). This discrepancy is apparently due to the fact that studies were based on the sugar intake of large populations and whole countries whichis difficult to determine, West, 1974 (13), and that the existance of a genetic sensitivity to high intake of sucrose between populations was overlocked.

Although our diabetic model is highly suggestive of the existance of a sensitivity to a high intake of refined sugar in producing diabetes, it cannot be applied to humans. The present study was carried out in order to study this theory in Yemenite immigrants in whom no diabetes was present upon their arrival to Israel and in whom no intermarriage with other ethnic groups has occurred. In order to see whether there are two groups among the "new immigrant Yemenites" - one who in the new environment will develop diabetes, and the other that will not and whether in the group in whom diabetes appeared there is a correlation between high refined sugar intake and diabetes, while in the other group which does develop diabetes, no such correlation exists.

MATERIAL AND METHODS

Four hundred and two Yemenites, 193 males and 209 females aged 30 years and over are included in the study. These Yemenites, born in the Yemen, immigrated to Israel 25 years ago and are living in 7 agricultural settlements,* (Table 1). About 65-75% of the settlers in each settlement were willing and participated in the study. Cases known to be diabetic or to suffer from vascular disease are not included in the study. The subjects came to the examination following an overnight fast. Venous blood was collected in heparin for glucose determination and in 1 mg/ml disodium EDTA for lipid studies after which 1 g. glucose per kg. body weight was given orally and blood was drawn after 30, 60 and 120 minutes, in heparinised tubes for glucose and insulin determination. A medical history was taken and a physical examination was made. A nurse trained in genetics took the genetic details and drew a genetic family tree.

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*Bekoa, Givat-Yearim, Ora, Shtulim, Tarom, Tzelafon and Yinon.

According to the ponderal index (P.I.) - height/$\sqrt[3]{\text{weight}}$ - the subjects were subdivided into overweight and underweight groups. As the median P.I. for the total population was for males 12.488 with a variance of 0.550 and for females 12.179 and a variance of 0.388. Subjects with P.I. of 12.4 and over were considered overweight while those with a P.I. under 12.4 underweight.

Glucose was determined using a Beckman glucose analyzer and insulin was determined by double antibody radioimmunoassay using the Amersham Insulin Kit. A glucose tolerance test was considered diabetic when the blood glucose following the load was 190 mg.% and over at 60 minutes and 140 mg.% and over at 120 minutes. It was considered normal when the blood glucose was under 160 mg.% at 60' and under 120 mg.% at 120'. Borderline cases were considered those with blood glucose values between 189 and 160 mg.% at 60 minutes and between 139 and 120 mg.% at 120'. The insulin response curves were classified both in the diabetics and non-diabetics, according to the time of their maximal response at 30, 60 or 120 minutes as well as flat curves. Statistical evaluations were carried out using the Student t-Test and X^2 (14).

In 306 Yemenites, 182 males and 122 females the blood lipids were studied as follows: For plasma lipid and lipoprotein determination, plasma was separated within a few hours. The presence of a chylomicron layer was recorded by inspection of plasma stored at $4^{\circ}C$ for 24 hours. Plasma lipid levels were determined by the autoanalyzer technique (15, 16). HDL cholesterol level was determined following heparin-$MnCl_2$ precipitation of VLDL and LDL (17). Paper electrophoresis of lipoproteins was performed as described by Lees and Hatch (18, 19). LDL cholesterol levels were calculated from the measured values of plasma cholesterol, plasma triglyceride and HDL cholesterol as described by Friedenwald et al (20). The calculated LDL cholesterol level was shown previously to reflect very accurately the true LDL

cholesterol level in an Israeli population examined by us in the Hadassah University Hospital, Eisenberg, 1976 (21).

Hyperlipoproteinemia was defined by plasma and lipoprotein lipid levels following the WHO panel recommendations (22), and using the cut-off criteria suggested by Fredrickson and Levy, 1972 (23). Accordingly, the type IIa was diagnosed in subjects with LDL cholesterol above 200 mg. %, and normal plasma triglyceride levels; type IIb insubjects with elevations of both plasma triglycerides and LDL cholesterol levels; and type IV in subjects with plasma triglycerides above 200 mg.% and normal LDL cholesterol. The more rare forms of hyperlipoproteinemia (types I, III and V) were not encountered in the present study.

The methodology for the dietary study was as follows: Each of the families selected was visited twice during the same week by an experienced nutritionist who had a detailed questionnaire and collected the necessary information from both husband and wife. On the first visit all the material concerning two weekdays (the 2 days preceding the visit) was noted down. On the second visit the data concerning Friday and Saturday - days with a much richer and more varied food pattern than weekdays - was collected.

The information assembled included: Menus of all meals and in-between snacks and the quantities of foods appearing in the above menus. The housewife showed the size of the portion which was translated into grams by the nutritionist who carried with her a portable scale. The weekly purchases of food for the whole family and number of persons in the family partaking regularly of the family meals was also recorded for control.

Averages of the dietary intake according to 34 food sub-groups were calculated separately for the diabetics, non-diabetic relatives and controls of the healthy families. The nutrients of each item were culled from the food composition table by Guggenheim et al, published by the College of Nutrition and Home Economics supplemented by material from Handbook 8, published by U.S. Dept. of Agriculture.

RESULTS

The percent of diabetic and borderline cases in the different age groups are shown in Table 1. In the total population there were 12.4% diabetics (13.9% in males and 12.4% in females) and 11.7% borderline cases (10.3% males and 14.0% females). The prevalence of diabetes increased with age in all age groups. Overweight results in an increase in the percent of diabetes in all the age groups in the female while in the male overweight results in an increase of diabetes in the age group of 55 plus only. The effect of overweight on the prevalence of diabetes was not significant for males, $X^2=0.4771$ P=n.s., but highly significant for females, $X^2=6.9452$ P/0.01.

The absolute blood glucose and plasma insulin values at 0, 30 and 120 minutes following the glucose load of the different types of insulin response curves with peaks at 30, 60 and 120 minutes are presented in Figure I-III. The percent of the insulin response curves with peaks at 30, 60 and 120 minutes as well as the flat curve in the non-diabetic and diabetic subjects is presented in Table 2. The delta insulin between the fasting level and that at 30, 60 and 120 minutes following the load in the different types of curves are presented in Table 3. In the underweight subjects 49.0% of the non-diabetics have a maximum insulin response at 30 minutes while in the diabetic subjects only 16.7%, while 44.0% of the non-diabetics and 38.9% of the diabetics have a peak at 60 minutes. 16.7% of the diabetic subjects

have a flat curve versus 2.0% in the non-diabetic subjects. In the overweight 35.6% of the non-diabetic subjects and 6.3% of the diabetics had a maximum response curve at 30 minutes. 48% of the non-diabetics and 56.3% of the diabetics have a delayed response with peak at 60 minutes.

It is noteworthy that except for the insulin curves with maximal response at 30' there is no significant difference in the extent of insulin response of the non-diabetic and the diabetic in the corresponding types of curves (Table 3). The fasting insulin in the diabetics was not significantly different from that of the non-diabetics in the underweight group while in the overweight group the fasting insulin of the diabetics was higher in the 120' peak curve and in the flat curves.

Table 4 details the absolute blood glucose levels following the oral glucose tolerance in the underweight and overweight non-diabetic subjects in the different age groups. No difference was noted in the blood glucose values at 60 and 120 minutes following glucose load with aging. It appears that females have lower blood glucose values than males but the difference is not statistically significant.

Table 5 details the insulin response following oral g.t.t. in the non-diabetic underweight and overweight subjects of the different age groups. It is apparent that the plasma insulin response in the different age groups vary inconsistently with age, and the differences are not significant. In a large proportion of the overweight group, especially in males, the insulin values following the glucose load are significantly higher when compared to the corresponding underweight groups.

Table 6 shows the ratio of the increase of blood glucose level from fasting levels/ the corresponding increase of insulin values from fasting levels at $\frac{1}{2}$ hr., 1 hr.

and 2 hrs. following the glucose load in the different types of insulin response curves. It is evident that the higher glucose insulin ratio in the diabetics at the different periods and in all types of insulin response curves are attributable to undue hyperglycemia, since insulin increments at these times were not different from those present in the normal glucose tolerance.

The correlation index of plasma triglyceride, plasma cholesterol and LDL and HDL cholesterol levels as related to age and sex in non-diabetic subjects is shown in Fig. 4. In both males and females: the regression analysis (r) for the increase of total cholesterol and of LDL cholesterol levels, with age, was significant, while for the TG level it was not significant. The regression analysis for the increase of HDL cholesterol level, with age, was significant for females, but not for males.

Mean plasma triglyceride, plasma cholesterol, LDL and HDL cholesterol levels and HDL/LDL ratio are shown in Table 7. The mean plasma triglyceride was higher in overweight males and females as compared to underweight, but significant only in overweight non-diabetic males. Plasma cholesterol levels were in general higher in overweight as compared to underweight subjects, but these differences were not statistically significant. Mean LDL cholesterol was variable among the groups, and significantly higher in overweight diabetic males. Plasma HDL cholesterol levels were in general lower in overweight subjects, but significant changes were noted only in non-diabetic males.

Significant increase of mean blood lipid levels between non-diabetic, diabetic and borderline subjects were noted with plasma triglycerides (underweight diabetic males and overweight diabetic females), plasma cholesterol (underweight diabetic males and overweight diabetic males) and plasma LDL cholesterol (overweight diabetic

males). The HDL/LDL cholesterol ratio was lower in overweight than in underweight subjects, significantly so only in the case of diabetics.

The incidence of hyperlipoproteinemia in non-diabetic, borderline and diabetic subjects is shown in Table 8. It is evident that in diabetic subjects, all three types of hyperlipoproteinemia were more common than in non-diabetic subjects. We are aware of the small number of cases of diabetics, but still we calculated the X^2: non-diabetic v. diabetic = 9.5472 $P < 0.05$. Mean plasma lipid and lipoprotein levels of subjects with normal lipoprotein profile and the three types of hyperlipoproteinemia encountered in the study population are shown in Table 9. As expected, LDL cholesterol levels were elevated in subjects with types IIa and IIb, and triglycerides in types IIb and IV when comparing hyperlipoproteinemic subjects to those with normal lipoprotein pattern, either in the non-diabetic, borderline, or diabetic subjects. It is however interesting to note that in diabetic subjects with hyperlipoproteinemia, the HDL/LDL cholesterol ratio was lower than in non-diabetics with respective lipoprotein profiles. These differences were significant for type IIa and IIb.

According to the genetic trees there were 44 families in which one or more cases of diabetes was present and 15 families with no diabetes. In the diabetic families there were 316 subjects, 132 males and 184 females. In the families with no diabetes there were 86 subjects, 42 males and 44 females. A dietary study was carried out in 20 diabetic men and their 20 non-diabetic first degree relatives and 20 matched controls from the families with no diabetes and in 18 diabetic women and in 20 matched 1st degree relatives and in 18 controls from the non-diabetic families. Table 10 details the total calories, the carbohydrates, fat and protein intake in the males and females of the diabetic, non-diabetic relatives and controls from the families with no diabetes.

The total calories and total carbohydrate intake in both males and females of the non-diabetic relatives was lower than that of the corresponding diabetic and healthy family groups, but significantly so only in females.

The total fat intake, the saturated fat intake as well as the linoleic acid intake of the diabetics was significantly higher when compared to their non-diabetic relatives. However, they were lower than those of the males in the healthy families. These differences were not noted in the female. Thus the differences of fat intake were not consistent.

There was no significant difference in protein intake between the different groups. The refined sugar intake was significantly higher in both male and female diabetic groups compared to their non-diabetic relatives. However, there was no significant difference in the intake between the diabetic groups and their respective healthy control groups. It is noteworthy that in the female healthy group the intake of refined sugar was even higher than that of the corresponding diabetic group.

DISCUSSION

Our diagnostic criteria for diabetes mellitus based on both a one hour value of 190 mg.% and a two hour value of 140 mg.% glucose following an oral glucose load satisfy the commonly used ones, Fajans and Conn, 1965 (24), Committee on Statistics, 1969 (25), Kobberling and Creutzfeldt, 1970 (26). The percent of diabetes in the examined population is 12.4% (13.9% in males and 10.0% in females). These results are not different from those observed in other studies outside Israel, Kobberling and Creutzfeldt, 1970 (26), Crombie, 1962 (27), Butterfield, 1964 (28), Gemuth et al, 1976 (29). The present results confirm our previous observations, Cohen, 1961 (1) that on

changing the environment this population, in whom 20 years ago almost no diabetes was detected, diabetes has now become prevalent in them as in other affluent communities.

The incidence of diabetes has increased with aging and was higher in individuals with overweight. It is a known fact that obesity alters significantly the glucose tolerance, West, 1966 (30). It is noteworthy that in this population the effect of overweight on the prevalence of diabetes was much more pronounced in females than in males. While in males the effect of overweight versus underweight on the increase in the prevalence of diabetes was observed in the older age group only, in females its expression was significant and evident also in the younger age groups.

In the underweight the prevalence of diabetes in males was higher than in females while in the overweight the prevalence in females almost equalled that in males. A higher diabetic male/female ratio was observed in our previous survey among the old settled Yemenites, Cohen, 1961 (1) and in other populations, Wilkerson and Krall, 1947 (31), Freedman et al, 1965 (32), Registrar General, England, 1965 (33), Blackard et al, 1965 (34). The role of overweight in the change of this sex ratio observed in the present study may explain the increase of diabetes among females that was found in recent decades in all age groups, Cohen, 1961 (1), Kenny and Chute, 1953 (35), Fitzgerald et al, 1961 (36) Simpson, 1969 (37).

Several authors reported an initially delayed insulin response to glucose stimulation as a common feature to all forms of diabetes mellitus from pre-diabetes, Cerasi and Luft, 1967 (38), Colwell and Lein, 1967 (39), the mildest forms, Seltzer et al, 1967 (40), and the clinical overt disease, Perly and Kipnis, 1967 (41), Kipnis, 1968 (42),

Lerner and Porte, 1972 (43). On the other hand, other investigators reported identical or greater insulin responses to i.v. or oral glucose in diabetic subjects, obese or non-obese, than in non-diabetics of comparable age, height and weight, Yallow and Bersen (44), Reaven et al, 1971 (45), Johansen, 1973 (46).

We have therefore classified the insulin response curves according to their time of maximal peak both in the non-diabetics and diabetics. Among the diabetics 83.3% of the underweight and 93.7% of the overweight have delayed insulin responses. It is noteworthy that 51% of the underweight non-diabetics and 64.4% of the overweight non-diabetics have also delayed insulin responses with peaks at 60 or 120 minutes following the glucose load. However, the extent of the insulin responses of the diabetics, at all times, in the corresponding types of insulin curve are not significantly different from the non-diabetics except for the cases with the 30 minutes maximal response. The higher glucose/insulin ratio in the diabetics compared to those of non-diabetics at the different periods of time, is attributable to undue hyperglycemia, since insulin increments at those times were not different in the diabetics from those present in the normal glucose tolerance. It appears that in order to explain this undue hyperglycemia one has to resort to "insulin resistance" or imply that the insulin molecule itself is structurally not intact. Overweight is frequently cited as a cause factor for insulin ineffectiveness, but this ineffectiveness was also evident in our non-obese diabetics.

Plasma cholesterol and LDL cholesterol levels are significantly lower in the non-diabetic Yemenite settler described here, as compared to the non-Yemenites reported recently by Eisenberg, 1976 (21), and Klorfajn et al, 1977 (47), whereas HDL cholesterol and plasma triglyceride levels do not differ. However, the non-Yemenites were not screened for impairment of glucose tolerance and represent an urban population.

The plasma cholesterol level in the non-diabetic Yemenite settlers now living in Israel for 25 years is higher than levels found soon after their arrival in Israel as reported by Toor et al, 1957 (48) and Brunner and Lobl, 1958 (49).

In our non-diabetic population - the regression analysis revealed significant increase of total cholesterol and LDL cholesterol levels with age while there was no such trend for an increase of plasma T.G. levels. This is in conformity with several authors who have reported an increase of the blood cholesterol level with age in both males and females, Marmorston et al, 1975 (50), Lewis et al, 1957 (51), while other investigators report no changes with age, Klorfajn et al, 1977 (47), Hays and Neill, 1964 (52). Overweight resulted in significant increases of plasma triglyceride levels and decreased HDL cholesterol levels in males but not in females.

Plasma triglycerides were increased in the diabetics, both males and females. The LDL cholesterol was increased in males while no consistant trend was noted in the HDL cholesterol levels.

Higher prevalence of hyperlipemia among diabetic subjects as compared to non-diabetic was reported by several investigators. Similarly, in this unique Yemenite population in Israel, the incidence of hyperlipoproteinemia among the diabetics was more than twice that of non-diabetics (27.7% and 11.0% respectively), while the percent of subjects with different types of hyperlipoproteinemia was similar to that reported by the other investigators, Bergquist, 1970 (53), Wilson et al, 1970 (54), Leren and Haabrekke, 1971 (55), Wood et al, 1972 (56), Schonfeld et al, 1974 (57). These observations, together with those discussed above, indicate that in the Yemenite population, an increase of plasma lipid levels occurred during the 25 years following their immigration to Israel, most probably due to the changing environment conditions.

However, the expression of diabetes in this unique population, at least as related to the plasma lipid and lipoprotein levels, were similar to that of other non-Yemenite diabetic populations.

Clinical and epidemiological studies show a consistent negative correlation between absolute plasma high-density lipoprotein (HDL) concentration and coronary risk, Berg and Børresen, 1976, (58), Miller and Miller, 1975 (59), Rhoads et al, 1977 (60). It has been postulated, Miller and Miller, 1975 (59) that the "protective" effect of HDL may relate to the role of HDL in the removal of cholesterol from peripheral tissues, Stein and Stein, 1976 (61), Miller et al, 1976 (62). Carew et al, 1974 (63) suggest that raised HDL concentrations may limit the uptake by smooth muscle of the arterial wall of LDL, a lipoprotein that contributes to the initiation and progression of the atherogenic lesions. The decisive factor in coronary risk is the relative HDL/LDL level at any given LDL concentration, Miller and Miller, 1975 (59). Our data (Table 7) suggests that in the underweight man and woman the HDL/LDL ratio is not significantly affected by diabetes, while diabetes in the overweight males and females results in a decreased HDL/LDL ratio, thus expressing the additive risk factor of diabetes to that of obesity in coronary disease.

The correlation of the high sucrose consumption with the increased prevalence of diabetes was suggested by us in 1961, Cohen et al (3). This was based on our observations on the prevalence of diabetes and sucrose consumption among the new immigrant Yemenites in Israel and the old settlers.

The subjects studied for dietary intake were aged 30 years and over so that all the examinees were born in Yemen. The group consisted of 20 diabetic males and diabetic females and corresponding numbers matched for sex, age and weight of their first degree

non-diabetic relatives and of individuals of the healthy families.

The dietary studies suggest that in the diabetics the refined sugar consumption was significantly higher than that of their non-diabetic relatives. On the other hand the refined sugar intake of control individuals of the healthy family group was not significantly different than that of their respective diabetic groups. This proves that in the humans, as well as in the laboratory, there are two sub-groups: one, on consuming large amounts of refined sugars will develop diabetes, while the other is not sensitive to a high refined sugar consumption and in spite of the fact that it consumes large amounts of refined sugar will not develop diabetes.

A common method to study the effect of diet on the prevalence of diabetes is to compare two populations in which there are significantly different diets. Investigators such as Campbell, 1963 (8), Cleave and Campbell, 1969 (64), Prior, 1971 (65), Shaefer, 1971 (66), and West, 1971 (9), reported a clear association between sugar intake and the prevalence of diabetes. However, other studies have pointed out that in other populations this relationship does not hold, Poon-King, 1968 (11), West, 1974 (13), Kahn, 1971 (12). The present study explains why such discrepancies may exist as the sensitivity to refined sugar intake may be different in different populations and also within certain groups of the same population.

It was claimed that increased prevalence of diabetes is associated with the increase of fat intake, West and Kalbfleisch, 1971 (9). The fat consumption in the present diabetic group studied was not different from that of the non-diabetic control groups.

The present study was made in agricultural settlements so that the factor of physical activity is more or less common to all of the examinees in their respective age groups.

Admittedly, our dietary studied group is small, although it suggests that in the human (as was observed in our genetic studies) that there are two genetic groups. One, that on a high refined sugar consumption develops diabetes while it's first degree relatives with the same genetic build up, on consuming smaller amounts of refined sugars will not develop diabetes. The second genetic group, that on consuming large amounts of refined sugars will not develop diabetes. To establish these results such a combined genetic and dietary study should be enlarged in this ethnic group and repeated in other ethnic groups.

Table 1. Prevalence of diabetes in the different age groups.

Age group	P. I. > 12.4					P. I. < 12.4					Total				
	No. examined	Borderline		Diabetic		No. examined	Borderline		Diabetic		No. examined	Borderline		Diabetic	
		No.	%	No.	%		No.	%	No.	%		No.	%	No.	%
MALE															
30 - 44	59	3	5.0	3	5.0	42	5	11.9	2	4.8	101	8	7.9	5	5.0
45 - 55	25	3	12.0	4	16.0	27	4	14.8	2	7.4	52	7	13.5	6	11.5
55 +	52	5	9.6	10	19.2	47	6	12.8	14	29.8	99	11	11.1	24	24.2
All ages	136	11	8.1	17	12.5	116	15	12.9	18	15.5	252	26	10.3	35	13.9
FEMALE															
30 - 44	28	2	7.1	0	0	37	2	5.4	3	8.1	65	4	6.2	3	4.6
45 - 55	13	1	7.7	0	0	32	6	18.8	5	15.6	45	7	15.6	5	11.1
55 +	16	2	12.5	1	16.3	24	8	33.3	6	25.0	40	10	25.0	7	17.5
All ages	57	5	8.8	1	1.8	93	16	17.2	14	15.1	150	21	14.0	15	10.0
											402	47	11.7	50	12.4

Effect of overweight on the prevalence of diabetes, males $X^2 = 0.4771$ P n.s.

females $X^2 = 6.9452$ P 0.01

Table 2. Types of insulin response following oral glucose tolerance (%).

	P. I. > 12.4					P. I. < 12.4				
	No. examined	Response Peaks at:				No. examined	Response Peaks at:			
		30'	60'	120'	Flat		30'	60'	120'	Flat
Non-Diabetic	159	49.0	44.0	5.0	2.0	146	35.6	48.0	14.4	2.0
Borderline	16	12.5	50.0	25.0	12.5	31	0	42.0	48.4	9.7
Diabetic	18	16.7	38.9	27.8	16.7	32	6.3	56.3	34.4	3.0

Table 3. Plasma Insulin levels (mean μ/ml $\pm$ S.E.) in diabetics and non-diabetics following oral glucose load.

Insulin curve with peak at:	P. I. > 12.4						P. I. < 12.4					
	No. examined	Fasting	Increase from fasting level 30'	60'	120'	Glucose 0 – 120'	No. examined	Fasting	Increase from fasting level 30'	60'	120'	Glucose 0 – 120'
30' Non-diabetic	78	8.7±0.7	34±3.2*	21±2.7*	8.0±1.5	401±6*	52	12±2.5	55±6.1†	28±6.4	22.4±6.8†	392±13.0
Diabetic	3	8.0±4.0	12.5±3.5	10±2.0	8.5±2.5	803±100	2	10±0	93±21†	67±0*†	102.0±48	885±94*
60' Non-diabetic	70	10.0±1.2	25.0±2.6	32.5±3.3	9.0±2.2	420±6.5*	71	14±1.3*	38±3.7	53±5.7†	19.0±3.3	426±10*
Diabetic	7	9.0±1.9	23.0±5.4	39.0±10.4	17.0±3.6	781±40	18	12.7±1.0	28±4.0	54±7.0	36±5.7*	783±44
120' Non-diabetic	8	8.0±3.7	4.0±2.0	10.0±4.9	57±12.6	389±3.5*	21	9.5±1.5	24±2.9†	42±5.8†	61±10.9	401±10*
Diabetic	5	10.0±3.7	14.0±7.0	28±11.2	48±12.7	744±53	11	14.0±2.8	25±2.5	42±5.5	65±6.4	784±40
Flat Non-diabetic	3	6.0±1.3	4.0±1.2	5±1.6	4±1.5	389±35	2	6.0±2.0	1±2.0	1.3±3.0	1.7±2.9	394±42*
Diabetic	3	11.0±3.7	3.0±1.7	0	1±2.0	1399±225*	1	19.0±2.2*	5±1.2	7.0±0.4	6.0±2.3	1036±52

* Diabetic v. Non-diabetic $P < 0.05$

† Overweight v. underweight $P < 0.05$

Table 4. Glucose tolerance test in non-diabetics of the different age groups.

Age group		P. I. > 12.4				P. I. < 12.4			
		No. examined	Time following the glucose load 0'	60'	120'	No. examined	Time following the glucose load 0'	60'	120'
30 - 44	M	53	86±1.5*	110±2.9*	86±2.4	35	86±1.8	118±3.7	94±3.3
	F	26	81±2.0	110±3.2	90±3.5	32	86±2.2	115±4.1	94±3.1
45 - 55	M	18	87±2.3	125±4.4	85±3.8	21	86±2.2	131±2.2	92±3.6
	F	12	87±1.9	116±6.7	86±5.3	21	83±2.7	118±4.5	95±3.5
55 +	M	37	87±2.3	121±2.9	82±3.1	27	90±3.4	122±4.9	95±4.3
	F	13	84±4.0	117±3.9	87±5.0	10	85±2.5	112±6.6	96±4.2

* mean ± S.E.

Table 5. Plasma Insulin response (mean μu/ml. ± S.E.) in non-diabetics following oral glucose load in different age groups.

Age group	P. I. > 12.4					P. I. < 12.4				
	No. examined	Fasting	Increase from fasting level 30'	60'	120'	No. examined	Fasting	Increase from fasting level 30'	60'	120'
MALES										
30 - 44	53	12.6±1.2	35.7±4.4	25.9±4.3	12.7±2.2	35	12.9±1.4	50.0±5.6†	46.4±4.9†	33.3±6.7†
45 - 55	18	9.8±1.2	27.2±6.0	26.0±6.2	8.5±5.0	21	17.0±2.4†	48.0±7.2†	56.2±8.0†	24.6±6.3
55 +	37	9.4±0.7*	29.0±3.2	34.2±4.2	11.1±2.0	27	15.9±5.8	37.8±7.8	38.0±5.6	25.0±10.0
FEMALES										
30 - 44	26	12.6±2.3	30.0±4.2	25.6±3.0	9.8±1.9	32	10.7±1.2	34.0±4.8	34.8±4.4	26.7±3.9†
45 - 55	12	11.9±1.7	23.0±3.4	28.2±7.4	17.5±6.6	21	9.9±1.3	29.4±8.0	25.0±5.2	14.5±3.9*
55 +	13	15.0±3.6	39.0±4.8	37.8±8.0	4.8±5.1	10	11.4±1.7	48.8±11.0	32.3±8.0	35.3±9.0*

* Versus older age group $P < 0.05$

† Underweight v. overweight $P < 0.05$

Table 6. Glucose/Insulin ratios in non-diabetic, borderline and diabetic glucose tolerance tests.

Time following Glucose load.	P. I. > 12.4			P.I. < 12.4		
	Non-diabetic	Borderline	Diabetic	Non-diabetic	Borderline	Diabetic
			Insulin Response - Peaks at 30'			
½ hr.	1.52±0.17	3.94±1.44	5.06±1.6	1.14±1.40		0.83±0.14
1 hr.	1.52±0.20	5.27±0.77	8.50±2.1	1.67±0.47		2.15±0.36
2 hr.	-0.60±0.84	-0.14±2.28	9.33±2.3	1.84±0.30		0.89±0.17
G 0-120	401±6.0	505±51	803±40	392±13		885
n	78	2	3	52		2
			Insulin Response - Peak at 60'			
½ hr.	2.25±0.94	8.50±3.9	7.98±2.12	2.76±0.54	3.38±0.79	6.03±1.1
1 hr.	1.54±0.23	6.65±2.8	5.01±0.92	1.04±0.22	2.14±0.48	3.93±0.28
2 hr.	-0.82±1.00	2.82±1.6	0.63±7.7	-0.01±0.62	1.44±0.72	5.28±1.61
G 0-120	420±6.3	585±31	781±40	426±10	552±29	783±44
n	70	8	7	70	13	18
			Insulin Response - Peak at 120'			
½ hr.	4.87±2.98	2.50±0.80	18.95±7.80	4.03±1.66	3.65±0.73	4.88±8.74
1 hr.	9.80±7.90	0.64±0.62	9.83±2.51	1.48±0.44	3.65±0.89	4.15±0.82
2 hr.	-2.94±3.60	0.79±0.17	3.08±0.71	0.57±0.12	0.88±0.16	2.42±0.52
G 0-120	389±3.5	540±16	744±53	401±10	560±24	784±40
n	8	4	5	21	15	11

Table 7. Plasma and lipoprotein lipid levels of non-diabetic, borderline and diabetic subjects.

	MALE						FEMALE					
	No. examined	Plasma T.G. mg/dl	Cholesterol (mg/dl) in: Plasma	LDL	HDL	HDL/LDL	No. examined	Plasma T.G. mg/dl	Cholesterol (mg/dl) in: Plasma	LDL	HDL	HDL/LDL
Underweight P. I. 12.4												
Non-Diabetic	72	96± 5.3	179± 2.9	113± 3.5	47± 1.9	0.462± 0.038	43	90± 3.6	183± 4.1	124± 4.8	43± 2.4	0.368± 0.022
Borderline	9	115± 18.0	188± 16.0	126± 13.7	41± 6.5	0.353± 0.057	4	81± 12.0	183± 11.3	122± 12.2	44± 3.3	0.387± 0.057
Diabetic	11	128± 9.5 *	211± 12.9 *	112± 6.3	49± 7.0	0.370± 0.050	1	103	199	133	45	0.338
Overweight P. I. 12.4												
Non-Diabetic	51	136± 8.0 +	186± 4.4	114± 5.0	39± 1.3 +	0.373± 0.02	46	101± 6.5	194± 5.0	137± 5.3	42± 1.6	0.328± 0.019
Borderline	13	164± 31.0	207± 14.6	140± 18.0	39± 2.7	0.327± 0.06	11	117± 17.0	227± 10.3	138± 9.6	47± 2.3	0.341± 0.003
Diabetic	13	177± 36	212± 11.6 *	133± 7.3 *+	36± 3.6	0.289± 0.005 *+	11	135± 14.0 *	199± 7.5	134± 10.4	35± 10.4	0.275± 0.014 *

* P 0.05 Diabetic v. Non-diabetic within the P.I. group.

\+ P 0.05 Overweight v. Underweight of the respective group

Table 8. Incidence of hyperlipoproteinemia among non-diabetic, borderline diabetic and diabetic subjects.

	No. examined	Lipoprotein Type		
		IIA	IIB	IV
Non-Diabetic	219	2.3 (5)*	0.9 (2)	7.7 (17)
Borderline	31	6.4 (2)	3.2 (1)	12.9 (4)
Diabetic	36	11.1 (4)	2.8 (1)	13.9 (5)
Diabetic + Borderline	67	9.0 (6)	3.0 (2)	13.4 (9)

* ( ) No. of subjects

X^2 Non-diabetic v. Diabetic = 9.5472 $P < 0.05$

Table 9. Plasma and lipoprotein lipid level among subjects with normal lipoprotein profile and with hyperlipoproteinemia.

Lipoprotein Pattern	T.G.	Cholesterol (mg/dl) in:			
		Plasma	LDL	HDL	HDL/LDL
		NON-DIABETIC			
Normal (195)	88±2.7	175±2.0	114±1.9	44±1.0	0.386±0.008
IIa (5)	101±11.1	274±3.1	232±10.0	44.6±3.2	0.257±0.027
IIb (2)	242±4.5	317±16.5	243±11.5	36±0.5	0.176±0.1
IV (17)	273±15.6	205±6.7	102±7.1	35.2±2.1	0.340±0.023
		BORDERLINE			
Normal (24)	89±6.7	177±7.0	116±5.7	42±3.6	0.362±0.035
IIa (2)	131±27	289±11.5	221±4.0	41±6	0.1829±0.03
IIb (1)	203	289	214	35	0.1636
IV (4)	461±129	244±43	108±20	59±13	0.458±0.10
		DIABETIC			
Normal (26)	116±8*	187±6.0	122±5.7	41±3.3	0.3515±0.037
IIa (4)	122±34	301±23.7	225±12.6	35±0.5	0.182±0.004*
IIb (1)	250	284	219	29	0.132
IV (5)	310±56.9	209±18.2	131±8	36±5.3	0.2666±0.028

* Non-diabetic v. Diabetic P/0.05

Table 10. Nutrients Per Head Per Day.

Men	No. of subjects	Age	P. I.	Calories	Mono + Dissach.	Carbohy-drates	Total Fat	Sat. F. Acid	Linoleic Acid	Protein
Diabetic	20	54.4±1.7	12.69±0.12	3563±147	170±9.5	485±22.4	128.5±7.1	42.9±3.3	39.2±2.8	117±5.1
Non-diabetic relatives	20	52.4±1.8	12.43±0.10	3272±137	127±6.4*	428±18.3	109.4±5.4†**	32.5±1.8*†	33.8±0.09*†	104±5.9
Healthy Family	20	51.9±2.4	12.70±0.11	3864±124	144.3±8.7	486±16.6	139.2±7.7	44.0±2.8	41.4±2.90	115±4.3
Women										
Diabetic	18	49.6±2.34	12.0±0.14	2807±95	151±13.8	384±16.0	98.8±5.6	30.7±1.6	29.0±3.05	86.6±2.3
Non-diabetic relatives	20	46.2±1.46	12.22±0.11	2461±113**†	93.1±6.7*†	301±11.8*†	105.0±5.6	30.6±1.6	42.0±3.05**†	75.5±2.3
Healthy Family	18	48.5±1.44	12.22±0.094	2760±63	164±6.9	385±9.9	96.2±4.0	27.7±1.2	31.4±1.5	80.4±2.1

* $P < 0.01$ v. Diabetic
** $P < 0.05$ v. Diabetic
† $P < 0.01$ v. Healthy Family

Cooperation with American Institute

As to the collaboration with the Nutrition Institute, U.S.D.A. In our original project we asked to budget the expenses of studying the lipids by Dr. Sheldon Reiser in the Carbohydrate Nutrition Laboratory of the Nutrition Institute, U.S.D.A., but this was not grated. However, on January the 2nd, 1977, Dr. Reiser visited us for a week and went over the data with us as to the prevalence of diabetes, blood lipids and the dietary intake. This he took back with him for presentation to his department.

In his letter of February 10, 1977, he wrote, "I think that while these data are preliminary and there are data from four more villages to compute, these results should be made known to our scientists and administrators here with a view toward continued support."

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